Synthesis and Characterization of C2–C3 Functionalized Indole Derivatives via Electron-Donor–Acceptor (EDA) Complexes

SYNOPSIS

SUBMITTED TO

(Faculty of Sciences)

UNIVERSITY DEPARTMENT OF CHEMISTRYB.N.MANDAL

UNIVERSITY MADHEPURA

SUBMITTED BY

NAME:- Randhir Kumar
PAT ROLL NO :- 00043/23
Class ROLL NO :- 07
COURSE WORK EXAM ROLL NO.: CHE-05/23
CONTACT NO:- 8084908734
M.Sc. Registration No. 08615/14

EMAIL ID:- randhirkumarbgp89@gmail.com

Synopsis of Research Work for Ph.D. Degree in the Faculty of Science(Chemistry)

Synthesis and Characterization of C2–C3 Functionalized Indole Derivatives via Electron-Donor–Acceptor (EDA) Complexes

a) Purpose and Need of the Study

Indole is a **privileged scaffold** in medicinal chemistry, found in numerous natural products, pharmaceuticals, and bioactive molecules. In particular, indole derivatives substituted at the 2- and 3-positions are ubiquitous in alkaloids and drug candidates, often crucial for biological activity. The indole nucleus can mimic biomolecular interactions and confer potent pharmacological properties, making it a valuable framework for drug discovery. Therefore, new methods to functionalize the indole ring at C2 and C3 are in high demand, as they enable rapid diversification of this scaffold for developing therapeutic agents and complex molecular libraries.

Despite indole's importance, **traditional C2 and C3 functionalization methods have significant limitations**. C3 position of indole is naturally nucleophilic and has been widely exploited in reactions with electrophiles, often requiring strong catalysts or harsh conditions. C2 position, however, is less reactive and typically demands **pre-activation** (such as N-protection or directing groups on the indole nitrogen) and **transition-metal catalysis** to achieve substitution. These conventional approaches (e.g. palladium or cobalt- catalyzed C–H activation) can suffer from poor selectivity, limited functional group tolerance, and environmental or cost concerns due to metal use. There is thus a clear *need for mild, efficient, and green methodologies* to install functional groups at indole's C2 and C3 positions. **Electron-donor–acceptor (EDA) complex** mediated reactions have recently emerged as a promising solution, enabling direct C–H functionalization under photochemical conditions **without added metal catalysts or oxidants**. In an EDA complex, an electron-rich donor (such as an indole or an amine) and an electron-deficient acceptor form a weak charge-transfer complex that can be activated by visible light to generate radical species. Such radicals can selectively add to the indole

ring, forging new bonds at C2 or C3 under **mild, catalyst-free conditions**. The proposed research leverages this modern strategy to address the challenge of indole functionalization in a sustainable and innovative way.

b) Details of the Project (Chapterization)

Chapter 1: Introduction and Literature Review – This chapter will introduce the indole framework and its significance in chemistry and biology. A thorough literature review will summarize known methods for C2 and C3 functionalization of indoles. Traditional metal-catalyzed routes (for example, palladium-catalyzed C–H activation or Friedel–Crafts type reactions) and their limitations (need for directing groups, harsh conditions, etc.) will be discussed. The review will then focus on recent advances in *metal-free* and *photochemical* approaches, highlighting the concept of **EDA complexes**. Key studies demonstrating EDA-complex enabled indole functionalization will be analyzed – for instance, Melchiorre and co-workers' pioneering 2015 report of a direct indole C2-alkylation via an EDA complex between indole and benzyl bromides under light. Other relevant examples, such as Glorius's use of pyridinium salt acceptors for indole C2 alkylation and visible-light induced indole functionalizations reported in recent reviews, will be reviewed. By the end of this chapter, the knowledge gap will be clearly identified: while EDA complexes have shown great potential, further exploration is needed to generalize this strategy for a broader range of **C2 and C3 functionalized indole derivatives**. The objectives and scope of the present work will be formulated in the context of this literature background.

Chapter 2: Synthesis of C2-Functionalized Indole Derivatives via EDA Complexes – In this chapter, the focus is on developing new methods to selectively functionalize the indole at the 2-position using EDA complex strategies. We will design reactions wherein an indole (acting as either donor or acceptor depending on substitution) forms an EDA complex with a suitable reaction partner to facilitate C2 bond formation. One approach involves **C2– alkylation**: for example, mixing 2-methylindoles (electron-rich at the 2-position) with electron-deficient benzyl halides to form an EDA complex that, upon photoexcitation, yields radicals which couple at C2. Hu *et al.* (2025) demonstrated that a π-electron-rich indole and an electron-poor benzylic bromide can form an EDA pair,

enabling **photoinduced radical cross-coupling** to forge a new C–C bond at C2. Adopting and extending this strategy, we will explore a variety of alkyl halides (benzyl bromides, α-halo carbonyls, etc.) to install diverse alkyl chains at the indole C2 position. Another route to C2 functionalization we will investigate is **C2–arylation** via EDA complexes – for instance, combining N-acyl indoles with electron-poor aryl diazonium salts (which can act as acceptors) to generate aryl radicals that attach at C2. Throughout this chapter, reaction optimization (light wavelength, solvent, concentration, and substituent effects) will be detailed. We will also examine the scope and limitations of the new C2-functionalization methods by testing various indole substrates (including unprotected vs. N-protected indoles) and functional group tolerance. The expected outcome is to establish a **versatile, metal-free synthetic route to 2- substituted indoles**, and each successful reaction will be compared with literature precedents to highlight improvements in efficiency or selectivity.

Chapter 3: Synthesis of C3-Functionalized Indole Derivatives via EDA Complexes – This chapter targets the complementary position (C3) of the indole ring, developing EDA-complex-mediated protocols for C3 bond formation. Indole C3-position is inherently reactive, but controlling its functionalization often requires directing strategies to avoid side reactions at C2 or N1. We will employ novel tactics such as **transient directing groups** in conjunction with EDA chemistry to achieve regioselectivity. For example, Luo *et al.* (2025) recently reported a **selective C3 arylation** of indole by using morpholine as a transiently bound donor at C2, forming an EDA complex that upon irradiation produced a radical at C3 which coupled with (hetero)aryl partners. Inspired by this, we will investigate the use of *in situ* indole adducts (amines or other Lewis bases) to occupy C2 and direct radical attack to C3. The formation of an EDA complex between the indole (or its cation- radical) and an arylating agent (such as aryl diazonium or nitroaryl halides) will facilitate the **C3–(hetero)arylation** under light. In addition to arylation, **C3–amination** will be explored using EDA complexes: Sui *et al.* (2023) demonstrated a visible-light driven, catalyst-free C–N bond formation on indoles at C2 or C3 by pairing indole with an N- aminopyridinium salt (electron-acceptor), generating amino radicals that add to the indole ring. We plan to adapt this method to achieve predominantly C3 amination by choosing appropriate substituents or reaction conditions (since C3 is usually

the favored site for electrophilic attack on indole). Chapter 3 will present the development of these C3- functionalization protocols, including substrate scope (varying indole substitution patterns and different amine/aryl coupling partners) and optimization results. The outcomes will be analyzed to understand electronic and steric factors that govern **site-selectivity (C3 vs C2)**. By the end of this chapter, we aim to establish reliable EDA-based methods to synthesize 3- substituted indole derivatives (such as 3-arylindoles and 3-aminoindoles) with high selectivity and in good yields, expanding the toolkit for indole derivatization.

Chapter 4: Characterization and Mechanistic Studies – This chapter will detail the **characterization of all newly synthesized indole derivatives** as well as investigations into the mechanisms of the EDA-complex reactions. Each functionalized indole product will be thoroughly characterized using spectroscopic and analytical techniques: ^*1H*/^13C Nuclear Magnetic Resonance (NMR) spectroscopy for structural confirmation, High-Resolution Mass Spectrometry (HRMS) for molecular weight and formula verification, Infrared spectroscopy for functional group analysis, and, where possible, single-crystal X- ray diffraction for unambiguous structure determination of key products. Special attention will be given to confirm **regioselectivity** (i.e. whether substitution occurred at C2 or C3 as intended) using 2D NMR techniques and comparison to literature data. In parallel, **mechanistic experiments** will be conducted to elucidate the role of EDA complexes in these reactions. UV-Visible absorption studies will be used to detect the formation of EDA complexes between the indole substrates and electron-deficient partners – the appearance of new charge-transfer bands or distinct color change upon mixing reagents can indicate EDA complex formation. We will perform light/dark control experiments to confirm that visible light activation is required, and run radical trapping experiments (adding a radical scavenger like TEMPO) to gather evidence for radical intermediates (suppression of product formation in the presence of scavenger would support a radical pathway).

Additionally, transient spectroscopy or electron paramagnetic resonance (EPR) may be employed to detect short-lived radical species or radical ions generated upon

photoexcitation of the EDA complex. Kinetic studies (monitoring product formation over time or using varying light intensity) could provide insight into whether the reaction rate correlates with the formation of the EDA complex absorption, thereby strengthening the proposed mechanism. By combining these studies, Chapter 4 will not only characterize the indole derivatives but also validate the **EDA-complex mechanism** – showing that the success of these functionalizations indeed hinges on the single-electron transfer (SET) induced by the donor–acceptor complex. This understanding may enable us to rationalize the reactivity trends observed in Chapters 2 and 3 (for example, why certain substituents orEDA pairs work better) and guide further improvement in reaction design.

Chapter 5: Conclusions and Future Outlook – The final chapter will summarize the key findings of the research and reflect on the significance of the developed methodologies. We will recapitulate how the **purpose of the study** has been met – by successfully synthesizing a variety of C2- and C3-functionalized indole derivatives through novel EDA-complex- driven reactions under mild conditions. The advantages of these methods (such as being metal-free, requiring only visible light and simple reagents, and showing broad functional group tolerance) will be highlighted, in comparison to traditional approaches. The chapter will also discuss the potential applications of the new reactions, for example in the late- stage functionalization of complex drug molecules or natural products, thereby opening avenues for medicinal chemistry. Any limitations encountered (such as substrate classes that did not perform well) will be noted, and **future research directions** will be proposed. Future work could include extending the EDA-complex strategy to other positions or heterocycles, exploring asymmetric versions of the reactions, or integrating the C2/C3 functionalization methods in the synthesis of target molecules of pharmaceutical interest.

Overall, the conclusion will assert how the study has contributed new knowledge to the field of organic synthesis and has laid the groundwork for further innovations in indole chemistry.

c) Hypothesis

Based on preliminary literature evidence, we hypothesize that **electron donor– acceptor complexes can facilitate selective radical functionalization at the C2 and C3**

positions of indole. In particular, pairing an electron-rich indole (or indole anion/enolate) with an electron-deficient partner will form an EDA complex that, upon visible-light irradiation, undergoes intramolecular single-electron transfer.

This process will generate radical species that **selectively couple at the indole C2 or C3 position**, enabling formation of new C–C or C–N bonds. We expect that by appropriately choosing the donor and acceptor components (e.g. indole substitution, type of halide or oxidant, presence of transient directing groups), the reaction conditions can be tuned to favor either C2 or C3 functionalization as desired. The overarching hypothesis is that **EDA complex photoactivation provides a robust, catalyst-free platform** to achieve indole derivatization that was previously challenging or impossible with conventional methods, delivering the target C2- and C3-functionalized indole derivatives in an efficient manner.

d) Methodology

To test the above hypothesis and accomplish the project goals, the following **methodology** will be employed:

1. **Selection and Preparation of Substrates:** We will begin by selecting representative indole substrates and reagents for functionalization. Indoles with various substituents (e.g. 2-methylindole, 3-methylindole, N–H indole, N-protected indoles) will be either procured commercially or synthesized if necessary. Likewise, potential electron-acceptor partners such as benzyl bromides, aryl diazonium salts, and N-aminopyridinium salts will be prepared. These choices are guided by literature precedent (for instance, using 2-methylindole for C2 alkylation with benzyl bromides, or unsubstituted indole with aminopyridinium for C3 amination).

2. **EDA Complex Formation and Reaction Setup:** For each envisioned transformation, we will combine the indole substrate (electron donor if electron- rich) and the chosen electron-acceptor in appropriate stoichiometric ratios in a suitable solvent (common solvents for EDA reactions include acetonitrile or dichloromethane due to their medium polarity and transparency to visible light). The reaction mixtures will be set up in **photoreactors with visible-light LEDs** (e.g. blue LED, 450 nm, 5–10 W) under inert atmosphere (nitrogen or argon) to prevent oxygen quenching of radicals. No external photocatalyst will be added, in line with the EDA complex strategy. We will monitor whether an immediate color change occurs upon mixing reagents, as an indicator of EDA complex formation (many EDA complexes exhibit a charge-transfer absorption that imparts a distinctive color).

3. **Optimization of Reaction Conditions:** Each reaction will be optimized by varying key parameters: light intensity and wavelength (to efficiently excite the EDA complex), reaction time, temperature (most will be run at ambient ~25–30 °C, but temperature can be adjusted if needed to improve yields), and solvent polarity. We will also explore the effect of additives: although the goal is **additive-free** conditions, in some cases a **base or acid** might be screened to see if it influences the formation or reactivity of the EDA complex (for example, a base might deprotonate indole to make it more electron-rich

donor, or an acid might activate an acceptor). Each trial will be monitored by thin-layer chromatography (TLC) or aliquot analysis via GC-MS to track the consumption of starting materials and appearance of products. The optimized conditions will be those that give the highest yield of the desired C2 or C3 functionalized indole with minimal side products.

4. **Isolation and Purification of Products:** After irradiation for the determined optimal time, the reactions will be quenched (e.g. exposed to air or diluted with solvent) and the crude mixture will be analyzed. Workup typically will involve solvent evaporation and extraction. The crude product mixtures will be purified by column chromatography on silica gel or by preparative thin-layer chromatography to isolate pure indole derivatives. Yields will be calculated based on the isolated mass of product relative to starting indole. If necessary, recrystallization will be used for final purification, especially if single crystals are needed for X-ray analysis.

5. **Product Characterization:** All purified products will undergo comprehensive characterization. NMR spectroscopy (500+ MHz) will confirm the structures – proton and carbon spectra will identify the presence of new substituents at C2 or C3 (e.g. distinct chemical shifts for substituents on the indole ring carbons). Correlation experiments like HSQC/HMBC will help assign which carbon (C2 vs C3) is bonded to the new group, verifying regioselectivity. High-resolution MS will provide molecular formula confirmation. Infrared spectra may show new bonds (e.g. C–N stretches for amine substitution). Where possible, a representative C2 and C3 functionalized product will be crystallized and analyzed by X-ray crystallography, unambiguously confirming the substitution pattern on the indole ring. These characterization data will be compiled in Chapter 4 to validate the successful synthesis of the target molecules.

6. **Mechanistic and EDA Verification Experiments:** To support the proposed EDA complex mechanism, we will perform targeted experiments: (**a**) UV-Vis spectroscopy of the indole + acceptor mixtures will be recorded to detect charge- transfer bands – a successful EDA complex often shows a new absorption band in the visible region that neither component shows alone. The wavelength of light used in reactions will correspond to this absorption if observed. (**b**) A control reaction will be run in the dark (covering the

vial with aluminum foil) to ensure no product forms without light; lack of reaction in the dark would confirm that light activation (and thus presumably EDA excitation) is required. (**c**) Radical trapping: adding 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) to the reaction is expected to capture radical intermediates; if the EDA-initiated reaction is indeed radical, the presence of such scavengers should significantly depress product yield or lead to TEMPO-adducts detectable by MS. (**d**) Variations in electron properties: we will observe that electron-rich indoles (with electron- donating groups) form EDA complexes and react more readily, whereas electron- poor indoles might not form EDA complexes as easily – such trends will be documented, as they align with the theory that the indole must act as donor in most cases. Similarly, altering the acceptor's electron affinity (e.g. using different substituents on a benzyl halide) will show how the EDA complex and reaction efficiency correlate. Collectively, these methodological steps ensure a robust exploration of the research questions, from practical synthetic execution to deeper understanding of the underlying photochemical mechanism.

e) Bibliography

1. Mondal, M.; Ghosh, S.; Lai, D.; Hajra, A. **C–H Functionalization of Heteroarenes via Electron Donor–Acceptor Complex Photoactivation**. *ChemSusChem* **2024**, *17*, e202401114. (Review article summarizing visible-light induced EDA complex strategies for heteroarene functionalization, highlighting the mild conditions and high functional group tolerance of these methods.)

2. Hu, Y.-Y.; Liu, Z.-L.; Xiang, H.-Y.; Chen, X.-Q.; Chen, K.; Yang, H. **C2–Benzylic C(sp^3)– H Alkylation of Indoles Enabled by Photoinduced, EDA-Complex-Mediated Radical–Radical Cross-Coupling**. *Org. Lett.* **2025**, *27*(37), 10359–10364. (Demonstration of a new open-shell methodology to obtain 2-alkylindoles under mild conditions by leveraging a π-rich indole donor and an electron-deficient bromide acceptor in an EDA complex.)

3. Luo, A.; Liu, W.; Yang, J.; Zhou, J.; Zhang, S.; *et al.* **Photoinduced EDA Complexes Enabled C3 (Hetero)arylation of Indoles Using Amine as a Transient Occupying Group**. *Org. Lett.* **2025**, *27*(36), 10024–10030. (Selective C3 arylation of

indole accomplished by a catalyst-free EDA approach; a transiently bound morpholine at C2 directs aryl radical attack to C3, illustrating a strategy to control regioselectivity in indole functionalization.)

4. Sui, J.; Yang, Z.; Li, S.; Chen, X.; Zhang, X.; Shen, Q.; Jiang, H.; Li, J. **Visible Light-Driven Catalyst-Free Amination of Indoles Initiated by Electron Donor– Acceptor Complexes**. *Chinese J. Chemistry* **2023**, *41*(12), 1485–1490. (Reports a metal-free, photocatalyst-free C–N bond forming reaction at C2 or C3 of indoles via an EDA complex between indole and N-aminopyridinium salts, with broad substrate scope and mild conditions.)

5. Lu, H.; Zhu, G.; *et al.* **Anticancer Molecule Discovery via C2-Substituent Promoted Oxidative Coupling of Indole and Enolate**. *iScience* **2019**, *22*, 214–228. (Introduction of this paper highlights the prevalence of C2, C3-disubstituted indole motifs in bioactive compounds and underscores the need for efficient synthetic access to such structures in drug discovery.)

6. Zhou, B.; Weng, Z.; *et al.* **Acid-Catalyzed 2-Alkylation of 3-Alkylindoles with Unactivated Alkenes**. *Frontiers in Chem.* **2022**, *10*, 860764. (Contains a comprehensive literature review on indole C2 functionalization, noting traditional requirements of N-protection and metal catalysis, and references early breakthroughs in EDA-complex mediated indole alkylation by Melchiorre (2015) and others. Used here as a secondary source to contextualize the development of metal-free methods.)

Signature of the Research Scholar